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(71) Applicant: ATRIX LABORATORIES, INC. [US/US]; 2579 Midpoint Drive, Fort Collins, CO 50525 (US).

(72) Inventors: DUNN, Richard, L.; 5021 Kitchell Drive, Fort Collins, CO 80524 (US). KRINICK, Nancy, L.; 801 North San Francisco Street, Flagstaff, AZ 86001 (US). COX, Mark, S.; 3565 Windmill Drive #P3, Fort Collins, CO 80526 (US). JOSEPHS, Kelly, R.; 311 East Mulberry Street, Fort Collins, CO 80526 (US).

(74) Agent: BRUESS, Steven, C.; Merchant, Gould, Smith, Edell, Welter & Schmidt, 3100 Norwest Center, 90 South Seventh Street, Minneapolis, MN 55402 (US).

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(54) Title: LIQUID POLYMER DELIVERY SYSTEM

(57) Abstract

The invention provides a liquid drug delivery system made of a low molecular weight, biodegradable, water-insoluble, liquid polymer or copolymer combined with an active agent, and optional additives such as a modifying agent. The polymer or copolymer has a sufficiently low molecular weight to maintain the polymer composition as a liquid before and after introduction into the body of an animal. The liquid compositions are administered to an implant site in liquid form and remain as a liquid *in situ* to provide controlled release of the active agent. Also provided are methods of forming the liquid delivery system and a liquid polymer matrix *in vivo*, and of using the formulations for release of an active agent *in vivo* for treatment in an animal including a human patient.

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LIQUID POLYMER DELIVERY SYSTEM

BACKGROUND OF THE INVENTION

Biodegradable polymers have been used for making drug delivery devices and a variety of other medical applications. In particular, thermoplastic or thermosetting polymers have been used to make sutures, surgical clips, staples, implants, among other devices, that retain their shape when inserted into the body. For a drug delivery device, the drug is generally incorporated into the polymer composition and formed into the desired shape, and then inserted into the body through an incision. Alternatively, these polymers as small, discrete, particles, have been injected into the body using a syringe.

Preferable to these methods is the use of a liquid polymeric composition which is injected into the body where it flows into a cavity or space, and coagulates or cures into a solid mass in situ. See, for example, U.S. Patent No. 4,938,763 to Dunn et al. For example, the polymeric composition may be a nonreactive thermoplastic polymer or copolymer dissolved in a water-miscible solvent, that solidifies in the body upon the dissipation of the solvent into the surrounding body tissues. The polymeric composition may also be formulated with reactive, liquid, oligomeric polymers that cure by crosslinking to form a solid mass, usually with the use of a curing catalyst. A biologically active material can be added to the liquid polymer system to form a drug delivery implant.

Although these liquid polymeric systems have proven to be beneficial in many respects, they lack certain desirable characteristics when used as controlled release, particularly sustained release, drug delivery systems. For example, as the solvent dissipates into surrounding tissue and the polymer coagulates to form a solid matrix, the active agent is trapped or encapsulated throughout the polymeric matrix. The release of the active agent then follows the general rules for the dissolution or diffusion of a drug from

within a polymeric matrix. However, high molecular weight substances may be extremely slow to release from a solid polymer matrix. This is a disadvantage, especially when a drug needs to be delivered over a relatively short period of time before the solid polymer has an opportunity to degrade.

Further, while avoiding the need for an incision, the liquid systems form a solid implant matrix that may cause trauma or irritation to the adjacent or surrounding tissue because of the differences in compliance of the soft tissue and the hard solid implant, or because of the change in isotonicity of the tissue around the implant due to the presence of the solvent. In addition, with certain drugs such as proteins, and cellular materials, the solvent may affect the activity of the drug by changing its tertiary structure or conformation.

Therefore, an object of the invention is to provide a biodegradable polymer composition that will provide sustained delivery of an active agent locally or systemically in the body, without the other ingredients of the composition having an adverse effect on the activity of the agent. Another object is to provide a polymer composition that is an injectable liquid and will maintain itself *in vivo* as a liquid matrix rather than a dense solid, that contains the active agent evenly distributed throughout.

SUMMARY OF THE INVENTION

These and other objects are achieved by the present invention directed to a liquid polymer composition for delivery of an active agent into the body of an animal, and a method for using the composition, for example, to treat a disease in an animal.

The polymer composition is composed of a low molecular weight, biodegradable, water-insoluble polymer

or copolymer combined with an active agent to form a liquid drug delivery system. The active agent may be a biologically-active agent, as for example, an antibacterial or antifungal agent for providing a therapeutic effect in the body.

The polymer or copolymer has a sufficiently low molecular weight to maintain the polymer composition as a liquid before and after introduction into the body of an animal. The *in vivo* polymer matrix provides controlled rate of release of the active agent. Preferred polymers include low molecular weight polycaprolactones, polylactides and polyglycolides, and copolymers thereof, as well as copolymers of such polymers with a water-soluble polymer such as poly(ethylene glycol), an ethylene oxide-propylene oxide block copolymer, a poly(amino acid), among others.

The composition may also include additives as desired. For example, a modifying agent may be included as a solvent for the polymer and to decrease the bulk viscosity and thereby increase the flowability of the polymer composition. The modifying agent may also function to control the rate of breakdown or degradation of the polymer matrix *in vivo* and/or the rate of release of the active agent from the matrix. Useful modifying agents include, for example, a polyhydroxyl alcohol such as a liquid polyethylene glycol (PEG) or glycerol, a vegetable oil such as soybean or peanut oil, or a limited amount of a nontoxic, biocompatible organic solvent that is miscible or dispersible in an aqueous medium such as N-methyl-2-pyrrolidone (NMP).

For delivery of an active agent to an animal, an effective amount of the liquid, biodegradable polymer composition is administered to the implant site in the animal whereupon the polymer matrix provides sustained delivery of the active agent *in vivo* over a period of about 1-30 days. Preferably, the composition is sterilized before being administered. The polymer

composition can be administered to the implant site by subcutaneous injection, intramuscular injection, intradermal injection, or direct insertion into the implant site, for example, using an about 18-25 gauge needle.

The active agent is gradually released from the polymer matrix *in vivo* by diffusion and/or by degradation of the polymer by hydrolytic and/or enzymatic action. Preferably, the liquid polymer matrix will remain essentially intact for a time effective to deliver an active agent, and/or facilitate healing including enhancing cell growth and/or tissue regeneration. The biodegradability of the polymer matrix and rate of release of the active agent from the polymer matrix *in vivo*, may be modified, for example, by varying the molecular weight and/or structure of the polymer or copolymer, by the character of the active agent, and by the inclusion of a modifying agent among other additives.

The present compositions advantageously provide a liquid delivery system for an active agent that will not adversely affect the activity of the agent, for example, by denaturation as found with solid, polymer-based implant materials made with a major amount (i.e., > 50%) of an organic solvent such as N-methyl-2-pyrrolidone, dimethyl sulfoxide, and the like. A further advantage is that the present polymer compositions are injectable liquids and do not require surgical incision for implantation. The polymer compositions in an aqueous environment will remain in liquid form and do not precipitate to form a dense, solid mass. As such, the liquid polymer implant provides for faster delivery of an active agent that is slow to release from a solid implant which is a desirable feature for delivery of a high molecular weight protein, oligonucleotide, and the like. Yet another advantage of the present liquid polymer

composition and implant matrix is that the liquid implant causes less tissue trauma or irritation because it is not a solid mass within tissue.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a biodegradable, liquid polymer composition for sustained, controlled delivery of an active agent *in vivo* in the body of an animal. After injection or insertion into the body, the polymer composition, which is substantially insoluble in body fluids and other aqueous media, will remain in liquid form as a discrete mass or matrix. The active agent, preferably homogeneously disbursed throughout the polymer matrix, is released into the body by diffusion and/or degradation of the polymer matrix by hydrolytic and/or enzymatic action.

Liquid Polymer System. Polymers useful according to the invention include low molecular weight, biocompatible polymers and copolymers that are liquid at room temperature (i.e., about 25°C), and the polymer composition remains as a liquid when administered *in vivo* to an animal including a human patient. The polymers are biodegradable, substantially water-insoluble, and can be administered into the body of an animal as a liquid polymer composition via a syringe and needle. Preferably, the polymers have a low degree of crystallization and a low degree of hydrogen-bonding. The polymers and copolymers of the polymer matrix are enzymatically or hydrolytically degraded *in vivo* into physiologically-acceptable products that can be resorbed, metabolized and/or excreted from the body of the animal.

As used herein, the term "liquid polymer composition" means that the polymer composition (*ex vivo*) is a liquid with low viscosity and has a consistency that facilitates injection through a syringe

and needle, preferably an about 18-25 gauge needle, preferably a 20-gauge needle. When brought into contact with an aqueous medium, e.g., body fluids, the polymer matrix does not form a solid implant, such as a gel or porous, dense material. Rather, on contact with an aqueous environment such as water or extracellular fluid, and the like, the *in vivo* composition, i.e., polymer matrix, remains as a discrete mass in the form of a liquid solution or suspension and maintains substantially the same consistency as the *ex vivo* polymer composition.

The polymer composition is biocompatible in that neither the composition nor the *in vivo* polymer matrix cause substantial tissue irritation or necrosis at the implant site. The polymers or copolymers are biodegradable, bioerodable and/or bioabsorbable within the body of an animal. The term "biodegradable" means that the polymers or copolymers and the polymer matrix will degrade over time by the action of enzymes, by hydrolytic action and/or by other similar mechanisms in the body. By "bioerodible," it is meant that the polymer matrix will erode or degrade over time due, at least in part, to contact with substances found in the surrounding tissue fluids, cellular action, and the like. By "bioabsorbable," it is meant that the polymer matrix will be broken down and absorbed within the body, for example, by a cell, a tissue, and the like.

Polymers that are suitable for use according to the invention generally include any having the foregoing characteristics. Examples of polymers useful according to the invention include low molecular weight polylactides (PLA), polyglycolides (PGL), polycaprolactones (PCL), polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthoesters, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates,

polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), and poly(maleic anhydride). Related copolymers or terpolymers, or combinations or mixtures of the listed polymers with other polymers may also be used. Preferred polymers and copolymers include a 25:75 poly(lactide-co-caprolactone) (PLC) (0.08-0.13 I.V.), a polycaprolactone triol (PCLT, m.w. 540); and poly(DL-lactic acid) (PLA, m.w. of 126-261).

Also useful are the foregoing polymers formed as copolymers or terpolymers with liquid forms of water-soluble polymers. Such water-soluble polymers include, for example, a low molecular weight poly(ethylene glycol) with a molecular weight (m.w.) of less than about 1,000, and other liquid, water-soluble polymers that maintain the foregoing polymers and copolymers in a liquid form at room temperature and when contacted with an aqueous medium.

Another useful water-soluble polymer is an ethylene oxide-propylene oxide block copolymer having an EO:PO ratio of about 70:30 and a m.w. of about 11,500 m.w. When copolymerized with the foregoing polymers, the resulting polymer composition remains liquid *in vivo*. Useful EO/PO copolymers are available commercially under the trademark PLURONIC™ (i.e., PLF-127 gel; BASF-Wyandotte), or the trademark TETRONIC™.

Also useful are copolymers of lactide or glycolide with di- or tri-methylene carbonates which are low molecular weight liquids. Examples of such copolymers include poly(lactide-co-dimethylene carbonate), poly(lactide-co-trimethylene carbonate), poly(glycolide-co-dimethylene carbonate), and poly(glycolide-co-trimethylene carbonate), among others.

An active agent (i.e., drug) is dissolved, dispersed or entrained in the polymer composition. The polymer composition contains about 20-99 wt-% of a low molecular weight liquid polymer, preferably about

50-95 wt-%; and about 1-80 wt-% of one or more active agent, preferably about 5-20 wt-%. After administration into the body, the active agent is gradually released from the polymer matrix by diffusion and/or by degradation of the polymer matrix *in vivo*. Thus, the polymer delivery system is an injectable implant.

The biodegradability of the polymer matrix, and the rate of release of the active agent from the polymer matrix *in vivo* can be modified and optimized by varying the polymer composition, molecular weight and/or concentration of the polymer or copolymer, including the use of different mole ratios of the constituent monomers (i.e., D,L-lactide versus caprolactone); by varying the concentration of the active agent; and by the addition of various additives, particularly modifying agents. Adjustments to the rate of release of the active agent can also be made by diluting the polymer or copolymer with a limited amount of less than about 50 wt-% of a compatible solvent such as N-methyl-2-pyrrolidone, dimethyl sulfoxide, and the like, preferably about 5-20 wt-%, and/or adding a modifying agent that will increase or decrease the hydrophilicity of the polymer formulation.

Varying Molecular Weight. The molecular weight of the polymer or copolymer is sufficiently low to maintain the polymer composition as a liquid before and after introduction into the body of an animal, yet achieve a suitable rate of release of the active agent from the polymer matrix *in vivo*. Molecular weight of the polymer or copolymer can be determined by gel permeation chromatography based on polystyrene standards, by end-group analyses, light-scattering, vapor-phase osmometry, solution viscosity such as inherent viscosity, or other methods known and used in the art. As used herein, "inherent viscosity" (I.V.) is measured in deciliters/gm (dL/gm) in chloroform or benzene.

If the release of the active agent is too slow or too fast from the polymer or copolymer of such a molecular weight, the rate can be varied simply by adjusting the molecular weight accordingly. This is achieved by using polymers prepared at the desired molecular weight or by hydrolyzing the polymer by known techniques in the art to reduce the molecular weight to the desired level. The hydrolysis can be carried out in a steam autoclave or in water at elevated temperatures (>50°C).

Varying the polymer structure. The backbone structure of the polymer or copolymer can be varied to contain hydrolyzable functional groups to facilitate hydrolytic or enzymatic degradation of the polymer matrix. For example, the polymer or copolymer backbone can be formed with repeating functional groups such as ester groups, urethane groups, amide groups, lactone groups, glycolide groups, carbonate groups, and the like.

The polymer or copolymer can also be modified in the end groups, either at the terminal ends of the polymers or on side-chains to the main structure to contain reactive groups that will affect the degradation rate of the polymer matrix *in vivo*. Such groups include hydroxyl, carboxyl or amine groups. For example, a poly(caprolactone) having a carboxylic end group will degrade *in vivo* at a faster rate than a poly(caprolactone) having a hydroxy end group or ester end groups. Useful end-group modified versions of these polymers include, for example, hydroxyl, carboxyl, amine, or ester. The foregoing end groups can be incorporated in the polymer or copolymer structure according to methods known and used in the art.

Active Agent. The liquid polymer compositions include an active agent, for delivery to adjacent or distant tissues and.or organs in the animal. As used herein,

the term "bioactive agent" means a drug, medicament, or other biologically-, physiologically-, or pharmaceutically-active substance capable of providing local or systemic biological, physiological or therapeutic effect in the body of an animal.

The active agent may be soluble in the polymer composition to form a homogeneous mixture, or insoluble in the polymer solution to form a suspension or dispersion. Upon implantation, the active agent preferably remains dispersed in the polymer matrix. The active agent is released into the adjacent tissue fluids, preferably at a controlled, sustained rate by diffusion of the active agent through the polymer matrix or by exposure of the active agent to the tissue fluids as the polymer degrades or erodes with time. The release of the active agent from the polymer matrix may be varied, for example, by the solubility of the active agent in an aqueous medium, the distribution of the agent within the matrix, the size, shape, solubility and biodegradability of the polymer matrix, and the like.

The liquid polymer composition includes the active agent in an amount effective to provide the desired level of biological, physiological, pharmacological, therapeutic effect in the animal. There is generally no critical upper limit on the amount of the active agent included in the polymer composition other than that dictated by the pharmacological properties of the particular active agent. The only limitation is a physical limitation for advantageous application, i.e., the active agent should not be present in such a high concentration that the consistency, or viscosity, and handling of the liquid composition is adversely affected. The lower limit of the amount of active agent incorporated into the polymer composition will depend on the activity of the active agent and the period of time desired for treatment.

A bioactive agent may stimulate a biological or physiological activity within the animal. For example, the agent may act to enhance cell growth and tissue regeneration, function in birth control, cause nerve stimulation or bone growth, and the like. Suitable biologically-active agents for use in the invention includes substances useful in preventing an infection systemically in the animal or locally at the implant site, as for example, anti-inflammatory agents such as hydrocortisone, prednisone, and the like; anti-bacterial agents such as doxycycline, gentamicin, penicillin, tetracycline cephalosporins, bacitracin, vancomycin, methicillin, cefazolin, and the like; antifungal agents such as nystatin, ketoconazole, clotrimazole, ivermectin, amphotericin B, griseofulvin, flucytosine, and the like; antiviral agents such as acyclovir, ribarivin, vidarabine, and interferons; antiparasitic agents such as quinacrine, chloroquine, and the like; immunomodulators such as bacterial, viral and parasitic vaccines, cytokines, and immunostimulators, and the like.

Also useful is a substance, or metabolic precursor thereof which is capable of promoting growth and survival of cells and tissues or augmenting the functioning of cells, as for example, a nerve growth promoting substance such as a ganglioside, a nerve growth factor, and the like; a hard or soft tissue growth promoting agent such as an osteoinductive growth factor, platelet-derived growth factor, insulin-like growth factor, transforming growth factor β, fibroblast growth factor, human growth factor, fibronectin (FN), human growth hormone (HGH), a colony stimulating factor, bone morphogenetic protein, and the like; protein growth factor interleukin-1 (IL-1), and the like.

Other useful substances include antineoplastic agents such as methotrexate, 5-fluorouracil, tumor-

specific antibodies conjugated to toxins, tumor necrosis factor, and the like; analgesic agents such as salicylic acid, acetaminophen, ibuprofin, flurbiprofen, morphine and the like; local anesthetics such as lidocaine, cocaine, benzocaine, bupivacaine, and the like; vaccines such as hepatitis, influenza, measles, rubella, tetanus, polio, parvovirus, rabies and the like; central nervous system agents such as a tranquilizer, β-adrenergic blocking agent, dopamine, and the like; hormones such as progesterone, follicle stimulating hormone, insulin, somatotropins, and the like; antihistamines such as diphenhydramine, chlorphencramine, and the like; cardiovascular agents such as digitalis, nitroglycerine papaverine, streptokinase and the like; anti-ulcer agents such as cimetidine hydrochloride, isopropamide iodide, and the like; bronchodilators such as metaproternal sulfate, aminophylline, and the like; vasodilators such as theophylline, niacin, minoxidil, and the like; and other like bioactive substances. The bioactive agent may also be an antihypertensive agent, an anticoagulant, an antispasmodic agent, or an antipsychotic agent. Additional examples of bioactive agents that may be used in the present invention are found in Applicant's corresponding U.S. Patent No. 5,324,519, issued June 28, 1994, the disclosure of which is incorporated by reference herein.

Once the polymer composition is placed into the implant site, the active agent is released into the adjacent tissue fluids, preferably at a controlled rate. This release may result from diffusion of the active agent through and out of the polymer matrix, and/or the degradation of the polymer matrix. Thus, the liquid polymer composition is useful as a delivery system of drugs, medicaments, other biologically-active agents and diagnostic agents to tissues adjacent to or distant from the implant site. The release of the active agent from the matrix of the composition may be varied, for

example, by the solubility of the active agent in aqueous tissue fluids, the distribution of the active agent within the matrix, the size, shape, solubility, and biodegradability of the polymer matrix, the type and amount of adjuvant and/or additive, and other like parameters.

Additives. The polymer composition may further include additives as desired. Useful additives include, for example, a modifying agent.

Modifying Agent. The polymers and copolymers may optionally be combined with an inert, non-reactive, biocompatible and physiologically-acceptable modifying agent which is compatible with the polymer or copolymer and active agent, and, preferably, a pharmaceutically-acceptable substance to act as a solvent to reduce the viscosity of the liquid polymer composition and provide a more injectable material. The modifying agent may also function to modify the rate of release of the active agent from the polymer matrix *in vivo*. Due to the low molecular weight of the polymer or copolymer of the composition, the release rate of the active agent from the matrix may be faster than desired for treatment. A modifying agent may be included to slow down the release of the active agent from the liquid polymer matrix *in vivo* by changing the hydrophilicity of the polymer matrix.

The modifying agent may be, for example, a low molecular weight organic substance which is water-soluble, water-miscible, or water insoluble (i.e., water immiscible). Useful modifying agents for the present polymer composition include, for example, fatty acids, triglycerides and other like hydrophobic compounds, and organic solvents. Suitable modifying agents include, for example, alkylesters of mono-, di-, and tricarboxylic acids such as 2-ethoxyethyl acetate,

methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols such as propylene glycol, polyethylene glycol (PEG), glycerol (glycerin), sorbitol, and the like; fatty acids such as behenic acid, caproic acid, caprylic acid, coconut fatty acid, dimer acids, heptanoic acid, isostearic acid, isovaleric acid, oleic acid, and pelargonic acid, and the like; vegetable oils such as peanut oil, soybean oil, sunflower oil, sesame oil, cotton seed oil, and the like; triesters of glycerol such as triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols such as cholesterol; alcohols such as C_6-C_{12} alkanols, 2-ethoxyethanol, and the like.

Although not preferred, an organic solvent may be added to the polymer in a minor but effective amount, i.e., about 5-50%, preferably about 5-20%, to dilute the polymer composition and/or reduce the viscosity. Examples of organic solvents suitable for use in minor amounts in the present compositions include methyl-2-pyrrolidone (NMP); 2-pyrrolidinone (2-pyrol); C_{2-6} alkanols; 2-ethoxyethanol; alkyl esters such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate; ethylene glycol diethyl ether; ethylene glycol dimethyl ether; propylene glycol; (S)-(-)-ethyl lactate; acetone; alkyl ketones such as methylethyl ketone; dimethyl-formamide; dimethyl sulfoxide; dimethyl sulfone; tetrahydrofuran; cyclic alkyl amides such as caprolactam; decylmethylsulfoxide; oleic acid; aromatic amines such as N,N-diethyl-m-toluamide; and 1-dodecylazacycloheptan-2-one. The preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidinone, and dimethyl sulfoxide, due to their solvating ability and their compatibility.

A modifying agent may be used singly or in combination with another such compatible modifier. Suitable combinations of modifying agents include, for example, glycerol/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, butylene glycol/adipic acid, and the like. Preferred modifying agents include glycerol (glycerin) and a vegetable oil that is preferably peanut oil or soybean oil.

The choice of modifying agent employed depends on the mixture of polymers and/or copolymers and active agent in the polymer system. The amount of modifying agent combined with the polymer or copolymer will vary according to the desired viscosity of the polymer composition and/or the release rate of the active agent from the polymer matrix *in vivo*. The composition can contain about 5-50% of one or more modifying agents, preferably about 10-15%.

Preparation of the Compositions. The polymer compositions are prepared by combining the liquid polymer or copolymer with one or more active agents, and optionally a modifying agent or other additives and adjuvants as desired, at room temperature (about 20-30°C). The liquid polymer composition is formulated to achieve a viscosity that maintains the polymer or copolymer and the active agent, and other optional ingredients, as a homogeneous mixture of ingredients.

The composition may be stored or packaged in containing means, for example, a vial, jar, pouch, syringe or other container made of glass, plastic or other compatible material.

Administration and Use of the Composition. The polymer compositions of the present invention are useful for delivering an active agent, i.e., a bioactive or diagnostic agent, into the body of an animal. The liquid polymer composition may be injected or inserted

into an implant site of the body of a human or other animal. The term "implant site" is meant to include a site, in or on which the polymer composition is administered, as for example, a soft tissue such as the dermis, muscle or fat, or a hard tissue such as bone. Examples of implant sites include a subcutaneous injection site under the skin or intramuscular into muscle; an intraperitoneal injection site in which the composition is injected into the peritoneal cavity; a tissue defect such as a tissue regeneration site; a void space such as a periodontal pocket, surgical incision or other formed pocket or cavity; a natural cavity such as the oral, vaginal, rectal or nasal cavities, the cul-de-sac of the eye, and the like; and other sites into which the polymer composition may be placed.

The liquid compositions may be administered using a syringe and needle. Preferably, the viscosity of the composition allows the use of an about 18-25 gauge needle, with delivery of about 2cc of the polymer composition into the implant site within 5-10 seconds.

The composition is preferably sterilized prior to its application into an animal. Sterilization may be achieved, for example, by gamma radiation or other ionizing radiation, by gas sterilization using, for example, ethylene oxide; sterile filtration, and other suitable sterilization procedures known in the art. Preferably, the composition is sterilized using gamma radiation, electron beam, or sterile filtration. The liquid polymer composition may then stored at about 0-30°C until use.

Upon contacting an aqueous medium such as body fluids in the adjacent tissues, the polymer composition which is essentially insoluble in an aqueous medium, maintains itself in liquid form as a discrete mass or matrix. The liquid polymer composition will persist as a viscous, cohesive mass in the implant site for a time

effective to facilitate healing and/or delivery of the active agent.

The polymer matrix will gradually degrade by the action of tissue fluids. The active agent is released from the polymer matrix into surrounding tissue fluids over time by diffusion and/or as the polymer matrix degrades from hydrolytic and/or enzymatic action. The gradual degradation of the polymer matrix permits the controlled delivery of the active agent into the surrounding tissue fluids. The release of the active agent will also depend on the physical characteristics of the agent, i.e., solubility, stability, and other like parameters. The polymer material will not interfere with delivery of the active agent, or healing of the defect or tissue regeneration, and may facilitate healing and tissue regeneration by action of the active agent released from the matrix.

The compositions are useful for delivering an active agent to an animal for a variety of applications. For example, an antibiotic substance may be delivered to treat a tissue defect in an animal, a growth factor can be delivered onto the surface of a bone to promote healing and regrowth of tissue in the defect, among other applications.

The liquid polymer compositions containing the active agent, and other additives as desired, may be varied according to the desired duration or time interval for maintaining the composition as a matrix within the implant site. To enhance cell growth and tissue regeneration, it is preferred that the polymer or copolymer has a molecular weight and structure that will maintain the polymer matrix as a discrete mass and facilitate degradation or disintegration of the matrix *in vivo* within the implant site at a rate effective to allow displacement of the polymer matrix by cell growth from the adjacent cells or tissue, preferably over an about 10-30 day period. For delivery of a bioactive

agent, it is preferred that delivery of the agent is maintained in a gradual sustained manner over the desired period, preferably about 3-4 days to 3-4 weeks.

Formulation of the polymer composition and *in vivo* administration will ultimately be according to the judgment and protocol of the patient's attending health care professional such as a physician, or if appropriate, a dentist. Choice of the particular formulation of ingredients will be made by the attending health care professional. The amounts and concentrations of ingredients in the composition administered to the patient will generally be effective to accomplish the task intended. If that task is to fill a void space of a bone or other tissue defect, an appropriate quantity of the liquid polymer composition will be prepared with an effective amount of active agent and other optional ingredients to accomplish this task. For administration of an active agent, the amounts and release rates will follow recommendations of the manufacturer of the active agent. Generally, the composition will contain a bioactive agent in an amount of about 0.01-400 mg per ml.

The invention will be further described by reference to the following detailed examples, wherein the methodologies are as described below. These examples are not meant to limit the scope of the invention that has been set forth in the foregoing description. Variation within the concepts of the invention are apparent to those skilled in the art. The disclosures of the cited references and patent documents throughout the patent application, are incorporated by reference herein.

EXAMPLE 1

Poly(DL-lactide-co-caprolactone) (PLC) with an inherent viscosity (I.V.) of 0.12 dL/g was mixed with

follicle stimulating hormone (FSH) to give liquid polymer formulations with 3% and 6% by weight of FSH.

The formulations were examined for *in vitro* release of the FSH. Each formulation was loaded into a 1cc tuberculin syringe. About 40-60 mg of each formulation was expelled into a scintillation vial that was pre-wetted with about 100 μL of 10 mM tris buffer (pH 7.4), and allowed to set for 1 minute. About 3 ml of 10 mM tris buffer (pH 7.4) was added to the vial, causing the polymer to form a film or discoidal-shaped implant. The polymer compositions remained as viscous liquid matrices in the buffer.

The vials were capped and placed into an environmental shaker at 37°C. The tris buffer receiving fluid was then removed and replaced with fresh buffer at designated time points (i.e., 1, 2, 3, 4, and 5 days). The buffer that was removed was analyzed for FSH content by fast protein liquid chromatography (FPLC).

The polymer compositions made with the 25:75 PLC showed an extended release of the FSH *in vitro*. Both of the 25/75 PLC polymer formulations (3% and 6% FSH) released FSH up to day 5. The 3% formulation gave an about 40% release on day 1, 80% on day 2, and 100% on days 5 and 6. The 6% formulation gave an about 40% FSH release on day 1, 78% on day 2, and 95% on days 5 and 6. The 25/75 PLC formulation containing 6% FSH released less FSH on a percentage basis than the 3% formulation.

EXAMPLE 2

The 3% FSH formulation made with the liquid 25:75 PLC, as described hereinabove in Example 1, was evaluated for delivery of FSH *in vivo* in sheep.

Test sheep were injected subcutaneously (s.c.) with either one dose (1 ml) of the liquid polymer (3% FSH) composition, or eight doses (1 ml each; twice daily for 4 days) of 3% FSH in saline. Untreated, control sheep were administered saline solution only.

The viscous nature of the polymer formulation required administration using a 1cc syringe with a Luerlock and 18-gauge needle. Warming the formulation in a dry oven at about 40°C for about 20 minutes decreased the viscosity of the formulation substantially.

The plasma levels of FSH and ovulation rates were monitored in both the test sheep and the control. The mean plasma levels (ng/ml) before and after treatment were 0.58 and 0.23 for the untreated (control) sheep, 0.30 and 0.32 for the sheep receiving the FSH/saline solution, and 0.52 and 1.60 for the sheep injected with the liquid polymer formulation. The elevated plasma levels were maintained for almost 60 hours. The ewes ovulated as a result of high plasma levels of FSH. The mean ovulation rate (number of corpora lutea) was 1.2 for the untreated (control) sheep, 3.0 for the FSH/saline-treated sheep, and 2.3 for the sheep receiving the liquid polymer formulation.

EXAMPLE 3

Low molecular weight polymer compositions were prepared with a 25:75 PLC having an inherent viscosity of 0.08 dL/g, a polycaprolactone triol (PCLT) having a molecular weight of 540 daltons, and a 25:75 PLC having an inherent viscosity of 0.13 dL/g. Dimethyl sulfoxide (5% by weight) was added to the 25:75 PLC formulation with the higher inherent viscosity to reduce its bulk viscosity and make it easier to inject the formulation using a syringe.

Each of the polymer compositions were separately loaded at 3% by weight with pseudorabies virus, porcine parvovirus, ovalbumin, and a transmissible gastroenteritis vaccine. The formulations were injected behind the ear into large test pigs, each about 200 pounds. The control pigs received an oil-in-water formulation. Serum was collected from each of the

test and control animals before treatment and at 1, 2, and 4 weeks after treatment, to determine the antibody titers against ovalbumin, transmissible gastroenteritis, and porcine parvovirus.

The formulations with the PCLT and 25:75 PLC produced antibody levels at least as high as the oil-in-water control against the pseudorabies virus. Those animals were then challenged with pseudorabies virus at 30 days post-injection. The test animals that received the polymer composition maintained weight at the same rate or higher than the control animals. This demonstrates the effectiveness of the polymer formulations in delivery of antigen since weight loss is proportional to the severity of the infection.

WHAT IS CLAIMED IS:

1. A biodegradable, liquid polymer composition, comprising:

(a) a biodegradable, water-insoluble polymer or copolymer having a molecular weight effective to maintain the polymer or copolymer as a liquid at room temperature; and

(b) an active agent;

the composition, when placed in an aqueous medium, remaining as a liquid matrix with the active agent distributed throughout;

the liquid polymer matrix capable of sustained, controlled release of the active agent over a period of about 1-30 days.

2. The biodegradable composition according to claim 1, wherein the polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthoesters, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), and copolymers or terpolymers thereof.

3. The biodegradable composition according to claim 2, wherein the polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, and copolymers and terpolymers thereof.

4. The biodegradable composition according to claim 3, wherein the polymer is selected from the group consisting of poly(DL-lactide) having a molecular

weight of about 126-261 daltons, poly(caprolactone) having an inherent viscosity of about 0.08-0.13 dL/gm, and poly(caprolactone triol) having a molecular weight of about 540 daltons.

5. The biodegradable composition according to claim 2, wherein the polymer is a copolymer or terpolymer with a water-soluble polymer selected from the group consisting of poly(ethylene glycol), poly(amino acid), poly(malic acid), polysaccharide, N-(2-hydroxypropyl)-methacrylamide, and ethylene oxide-propylene oxide block copolymer.

6. The biodegradable composition according to claim 5, wherein the copolymer is poly(caprolactone-co-ethylene glycol), poly(lactide-co-ethylene glycol), or poly(glycolide-co-ethylene glycol).

7. The biodegradable composition according to claim 2, wherein the copolymer is poly(lactide-co-dimethylene carbonate), poly(lactide-co-trimethylene carbonate), poly(glycolide-co-dimethylene carbonate), poly(glycolide-co-trimethylene carbonate), or any combination thereof.

8. The biodegradable composition according to claim 2, wherein the polymer or copolymer contains a terminal end group or side-chain group selected from the group consisting of a hydroxyl, carboxyl, and amine.

9. The biodegradable composition according to claim 1, wherein the active agent is a biologically active agent selected from the group consisting of anti-inflammatory agent, antimicrobial agent, antiparasitic agent, anti-neoplastic agent,

analgesic agent, antipsychotic agent, anaesthetic agent, vaccine, central nervous system agent, cytokine, growth factor, hormone, antihistamine, osteoinductive agent, cardiovascular agent, anti-ulcer agent, bronchodilating agent, vasodilating agent, birth control agent, fertility-enhancing agent, and immunomodulating agent.

10. The biodegradable composition according to claim 9, wherein the active agent is an antimicrobial agent selected from the group consisting of antibacterial agent, antifungal agent, and antiviral agent.

11. The biodegradable composition according to claim 9, wherein the immunomodulating agent is a vaccine.

12. The biodegradable composition according to claim 1, wherein the active agent is a growth factor selected from the group consisting of osteoinductive growth factor, platelet-derived growth factor, insulin-like growth factor, transforming growth factor β, fibroblast growth factor, human growth factor, human growth hormone, colony stimulating factor, and bone morphogenic protein.

13. The biodegradable composition according to claim 1, further comprising a modifying agent.

14. The biodegradable composition according to claim 13, wherein the modifying agent is effective in reducing the viscosity of the polymer composition, modifying the rate of release of the active agent from the composition, modifying the rate of degradation of the liquid polymer matrix, or a combination thereof.

15. The biodegradable composition according to claim 13, wherein the modifying agent is selected from the group consisting of an ester of a monocarboxylic acid, ester of a dicarboxylic acid, ester of a tricarboxylic acid, polyhydroxy alcohol, fatty acid, vegetable oil, glycerol triester, sterol, and alcohol.

16. The biodegradable composition according to claim 15, wherein the modifying agent is selected from the group consisting of 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, propylene glycol, polyethylene glycol, glycerol, sorbitol, behenic acid, caproic acid, caprylic acid, coconut fatty acid, dimer acids, heptanoic acid, isostearic acid, isovaleric acid, oleic acid, and pelargonic acid, peanut oil, soybean oil, sunflower oil, sesame oil, cotton seed oil, triglyceride, epoxidized soybean oil, cholesterol, a C_6-C_{12} alkanol, and 2-ethoxyethanol.

17. The biodegradable composition according to claim 13, wherein the modifying agent is an organic solvent selected from the group consisting of N-methyl-2-pyrrolidone, 2-pyrrolidinone, a C_{2-6} alkanol, and dimethyl sulfoxide.

18. The biodegradable composition according to claim 13, comprising about 20-99 wt-% polymer, about 1-80 wt-% active agent, and about 5-50 wt-% modifying agent.

19. The biodegradable composition according to claim 1, wherein the composition is injectable via a syringe and needle.

20. The biodegradable composition according to claim 1, wherein the aqueous medium is tissue fluid in the body of an animal.

21. A method of delivering an active agent to an animal, comprising:

administering to an implant site in the animal, an effective amount of a liquid, biodegradable polymer composition, comprising:

(a) a biodegradable, water-insoluble polymer or copolymer having a molecular weight effective to maintain the polymer or copolymer as a liquid at room temperature; and

(b) an active agent;

wherein the composition remains as a liquid matrix *in vivo* with the active agent distributed throughout; and the polymer matrix provides sustained delivery of the active agent *in vivo* over a period of about 1-30 days.

22. The method according to claim 21, wherein the liquid polymer matrix remains essentially intact for a time effective to enhance cell growth, tissue regeneration, or a combination thereof.

23. The method according to claim 21, further comprising sterilizing the composition prior to administering the polymer composition to the animal.

24. The method according to claim 21, wherein the polymer composition is administered to the implant site by subcutaneous injection, intramuscular

injection, intraperitoneal injection, intradermal injection, or direct insertion into the implant site.

25. The method according to claim 24, wherein the polymer composition is administered by an about 18-25 gauge needle.

26. The method according to claim 21, wherein the active agent is a biologically-active agent.

27. The method according to claim 26, wherein the active agent is effective for treating a tissue in the animal.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/00105

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP,A,0 635 272 (ETHICON INC.) 25 January 1995 see claims 1-7 see column 4, line 7 - line 53 ---	1-4, 7-10,13, 19-26
P,X	EP,A,0 635 531 (ETHICON INC.) 25 January 1995 see claims 1-5 see column 3, line 3 - line 17 see column 3, line 45 - line 57 see column 4, line 39 - line 51 -----	1-3,9, 10,12, 17,19-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/00105

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-635272	25-01-95	CA-A-	2128361	21-01-95
		JP-A-	7166042	27-06-95
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